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Original article

SNP-array based whole genome homozygosity mapping: A quick and powerful tool to achieve an accurate diagnosis in LGMD2 patients☆

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ABSTRACT

A large number of novel disease genes have been identified by homozygosity mapping and the positional candidate approach. In this study we used single nucleotide polymorphism (SNP) array-based, whole genome homozygosity mapping as the first step to a molecular diagnosis in the highly heterogeneous muscle disease, limb girdle muscular dystrophy (LGMD). In a consanguineous family, both affected siblings showed homozygous blocks on chromosome 15 corresponding to the LGMD2A locus. Direct sequencing of CAPN3, encoding calpain-3, identified a homozygous deletion c.483delG (p.Ile162SerfsX17). In a sporadic LGMD patient complete absence of caveolin-3 on Western blot was observed. However, a mutation in CAV3 could not be detected. Homozygosity mapping revealed a large homozygous block at the LGMD2I locus, and direct sequencing of FKRP encoding fukutin-related-protein detected the common homozygous c.826 C > A (p.Leu276Ile) mutation. Subsequent re-examination of this patient's muscle biopsy showed aberrant α-dystroglycan glycosylation. In summary, we show that whole-genome homozygosity mapping using low cost SNP arrays provides a fast and non-invasive method to identify disease-causing mutations in sporadic patients or sibs from consanguineous families in LGMD2. Furthermore, this is the first study describing that in addition to PTRF, encoding polymerase I and transcript release factor, FKRP mutations may cause secondary caveolin-3 deficiency.

1. Introduction

The limb girdle muscular dystrophies (LGMD) are a clinically and genetically heterogeneous group of primary muscle disorders characterised by progressive weakness and wasting, predominating in muscles of the pelvic and shoulder girdle, with occasional involvement of the myocardium [1,5]. To date, 15 genes for autosomal recessive LGMD (LGMD2) have been identified. Because of the broad phenotypic variability both within groups and within families, delineation of genotype-phenotype correlations between these different subtypes is challenging. The accurate diagnosis can only be made by molecular genetic analysis, which is usually guided by protein analysis in a muscle biopsy whenever a decrease of any of the known LGMD2 proteins can be documented [1,5]. In addition, in the past years muscle magnetic resonance imaging (MRI) has been applied increasingly to determine distinct patterns of muscle involvement, which may point to a specific genetic subtype [3,11]. Moreover, it has been shown that it can be helpful to consider the geographical and ethnic origin of an affected individual in the differential diagnosis because of the occurrence of founder mutations in some subpopulations [5]. In particular,

☆ Accession codes: GenBank reference sequence accession numbers: *FKRP* mRNA, NM_001039885.2. *CAPN3* mRNA from all isoforms was combined, NM_000070, NM_024344, NM_173087, NM_173088, NM_173089, NM_173090, NM_212464, NM_212465, NM_212467. *PTRF* mRNA, NM_012232.4. *CAV3* mRNA, NM_033337.1.

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homozygous mutations can generally be expected to underlie the disease in consanguineous families and in patients whose ancestors originate from the same geographic area. However, the disease causing mutations still remain undetected in a large number of LGMD2 patients [1,12].

Recent molecular genetic studies have shown considerable progress in the identification of recessive disease causing genes using the positional cloning/candidate approach by homozygosity mapping [2,7]. By definition, homozygosity mapping, also known as autozygosity mapping, tests the assumption that a homozygous mutation in a recessive disease is identical by descent by segregating twice to the affected person from a common ancestor through both the maternal and paternal line [7]. The value of single nucleotide polymorphism (SNP) array-based homozygosity mapping, i.e. an indirect DNA analysis as a first step to the identification of a disease-causing mutation, has recently been evaluated by Hildebrandt et al., who retrospectively studied 72 individuals carrying known homozygous mutations and originating from both inbred and outbred populations [7].

Here we show that SNP-array-homozygosity mapping used in an affected individual only can guide molecular genetic testing in LGMD2, if there is known consanguinity of the parents.

2. Materials and methods

2.1. Patients

The present study included a consanguineous Turkish family (here called MD1) with two sibs affected with LGMD2, and another Austrian patient (here called MD2) with sporadic LGMD and known consanguinity of the parents. Clinical and electrophysiological studies followed standard methods and were performed with written informed consent and approved by the local Ethical Committee of the Medical University of Graz, Austria.

Two healthy unrelated individuals from an outbred population were selected as controls to compare 10 K and 250 K SNP array data.

2.2. Muscle biopsy

A muscle biopsy specimen was obtained from the gluteus medius muscle of patient MD2. Part of the muscle biopsy was fixed in formaldehyde and embedded in paraffin and the rest was rapidly frozen in isopentane cooled in liquid nitrogen. Serial transverse cryostat sections were processed using conventional histological stains and histochemical reactions, as previously described [14].

Immunohistochemistry was performed for dystrophin (N-terminus, rod domain, and C-terminus, Novocastra, UK), α-sarcoglycan (Novocastra, UK), β-sarcoglycan (Novocastra, UK), γ-sarcoglycan (Novocastra, UK), δ-sarcoglycan (Novocastra, UK), dysferlin (Novocastra, UK), merosin (Novocastra, UK), emerin (Novocastra, UK) on frozen, acetone-fixed sections, and later on for α-dystroglycan (clone VIA4-1, Upstate Biotechnology, USA) on formalin fixed and paraffin embedded tissue.

2.3. Immunoblotting

Frozen muscle samples (~20 to 30 mg) were quickly weighed and homogenized with 1× Laemmli buffer [9]. The samples were incubated at 95 °C for 10 min and centrifuged at 13,200 × *g* for 1 min before 10 μl aliquots of the supernatants (equivalent to 2.5 mg tissue) were applied to each lane. Electrophoresis, transfer, and immunological detection were performed as previously described [16]. The following antibodies were used: mouse monoclonal antibodies against caveolin-3 (Santa Cruz, USA), lamin A/C (Santa Cruz, USA), telethonin (BD Biosciences, Austria), calpain-3 (Leica, Germany) and α-dystroglycan (Millipore, Austria) as well as horseradish-conjugated goat anti-mouse immunoglobulins (DAKO, Denmark).

2.4. Genotyping and identification of homozygous regions

In order to define the molecular genetic basis of the disease regions of homozygosity in the LGMD2 patients, a whole genome scan using Affymetrix SNP arrays was carried out. Genomic DNA samples from patients and unaffected sibs from families MD1 and MD2, and a control sample were hybridized to GeneChip® Human Mapping 10 K XbaI 142 2.0 arrays (Affymetrix, Santa Clara, CA, USA) using the protocols recommended by the manufacturer. Samples from patient MD2, her healthy sib, and from a healthy control were subsequently also hybridized to GeneChip® Human Mapping NspI 250 K arrays. Genotypes of both array types were called using GeneChip Genotyping Analysis Software (Version 4.1) and default thresholds. The overall call rate of each array succeeded 95% or more.

The SNP results of family MD1 and MD2 were then further analyzed using a self developed Java-based tool (eHoPASA – Easy Homozygosity Profiling of Affymetrix SNP Arrays) which had been designed to quickly extract genome wide regions of homozygosity which may harbor the disease gene. The software accepts Affymetrix SNP array data and generates result files with homozygosity profiles, as well as the underlying genotyping data for these files. Single occurrences of genotyping failure discovered as heterozygosity, or undetermined genotypes ("no calls"), are ignored when at least seven neighboring genotypes on each side are homozygous [15]. We arbitrarily defined a homozygous region on the occurrence of at least 5 or more consecutive homozygous SNPs (10 K array) and 50 SNPs (250 K array) by the user-selectable parameter in the program. The generated homozygosity profiles were plotted across the entire human genome using the R statistical software package [13]. In addition to other software programs [15] our tool was adapted to quickly visualize the LGMD2 loci by inclusion of the physical positions of the LGMD2 loci and to use the local computer infrastructure. All analyses are based on human reference sequence HG 18 (NCBI Build 36 Version 1) genome assembly annotations. The eHoPASA software itself and R programming code for plotting of the homozygosity profiles will be freely available for download (http://ehopasa.sourceforge.net).

2.5. Mutation analysis

All exons and exon-intron bounderies of CAPN3 [OMIM 114240] (MD1) and CAV3 [OMIM 601253], PTRF [OMIM 603198] and FKRP [OMIM 606596] (MD2) were screened for mutations. PCR conditions were as follow: 20 ng of genomic DNA, 5 μl HotStarTaq Mastermix (QIAGEN GmbH, Hilden, Germany) and primer (10 pmol each) in a total volume of 10 μl. Cycle conditions were as follows: initial denaturation for 12 min at 95 °C; 35 cycles of 45 s denaturation at 95 °C, 30 s of annealing at 57 °C and 30 s of primer extension at 72 °C; and a final extension for 10 min at 72 °C. PCR products were purified with filter plates (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany) and directly sequenced with automated sequencer using BigDye Terminator v3.1 (ABI 3730 Genetic Analyzer, Applied Biosystems, Foster City, CA). Sequencing analysis was carried out using the SeqScape Software 2.5 (Applied Biosystems, Foster City, CA).

3. Results

3.1. Family MD1

The two patients, whose healthy parents are first cousins, initially complained about running and walking difficulties and

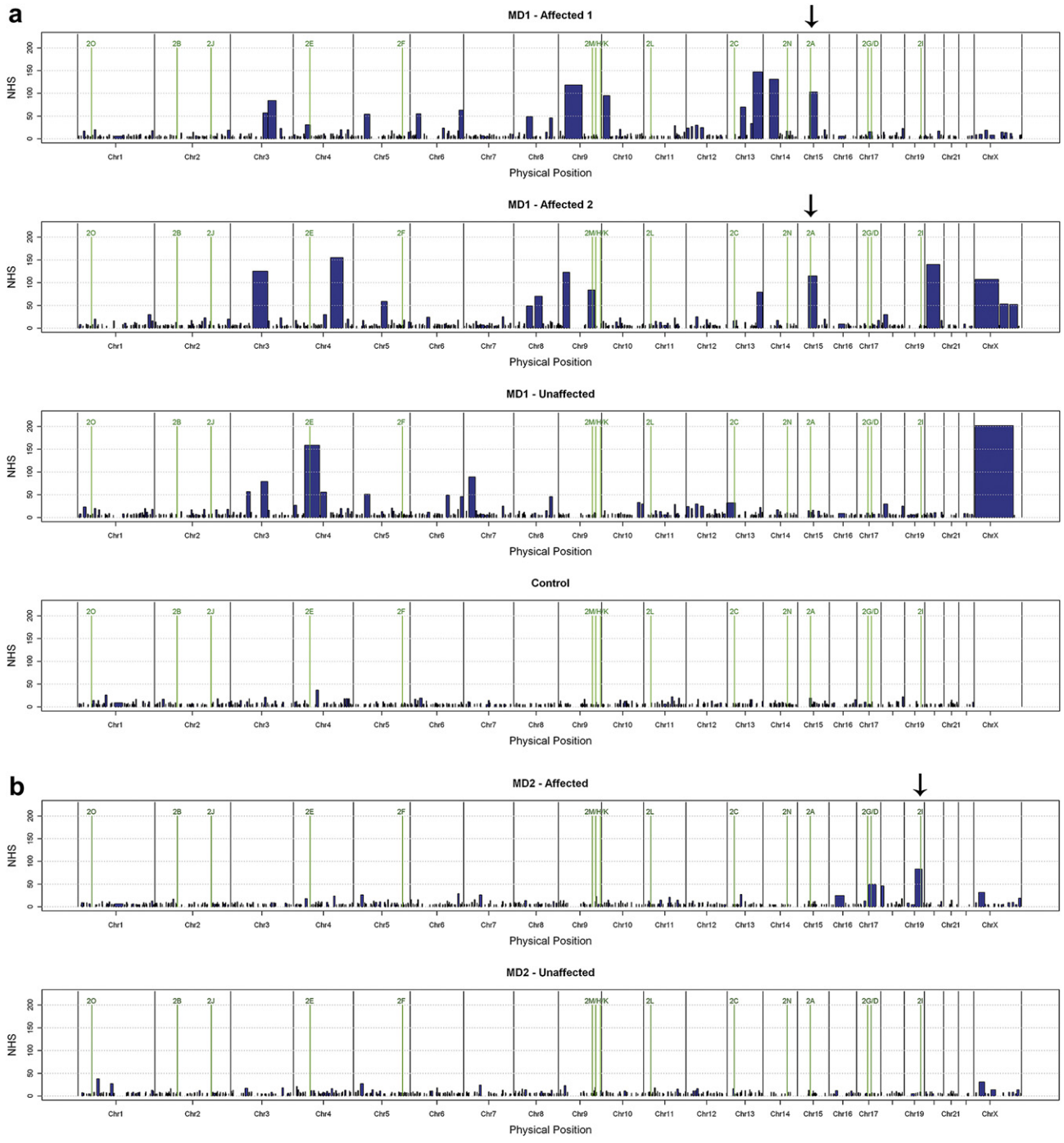

Fig. 1. Homozygosity profiles. The intervals of homozygosity (blue blocks) are plotted across the genome for each individual. The chromosomal positions of the homozygous intervals are indicated on the *x*-axis, the length of each homozygosity profile is defined by the number of basepairs (bp). The *y*-axis shows the number of homozygous SNPs (NHS). The physical positions of the LGMD2 genes (subtypes 2A-2O) are included and shown in green color. a. Homozygosity profiles for three individuals of family MD1 and a control sample (10K-Affymetrix SNP array), first and second line = affected individuals, third line = unaffected sib, forth line = control individual with no consanguinity of the parents: no homozygous blocks can be detected in the control individual. The arrow indicates the position of the mutated gene. b. Homozygosity profiles (10K-Affymetrix SNP array) of patient MD2 (first line) and her healthy sib (second line). Because of the more distant parental relationship the number of peaks is lower than in the individuals of family MD1. The arrow indicates the position of the mutated gene. c. Homozygosity profiles (250 K Affymetrix SNP array) of patient MD2 compared to a control individual with no consanguinity of the parents.

problems in climbing stairs starting at the age of 9 and 15 years, respectively. On examination there was symmetric weakness and wasting of the limb girdle muscles predominating in the pelvic girdle and in the proximal lower limbs muscles with the thigh adductors more severely affected than the quadriceps muscles. Serum creatine kinase (CK) levels were markedly increased up to 5500 and 12,000 U/L (normal values < 170 U/L). Electromyography (EMG) showed a chronic myopathic pattern and nerve conduction studies were within the normal range. These results established the diagnosis of LGMD2.

Muscle biopsy was not done. Instead, DNA was collected from the parents, the two patients, and the healthy sibs after informed consent. A whole genome scan using 10 K Affymetrix SNP arrays was carried out. We analyzed the haplotypes of the affected and

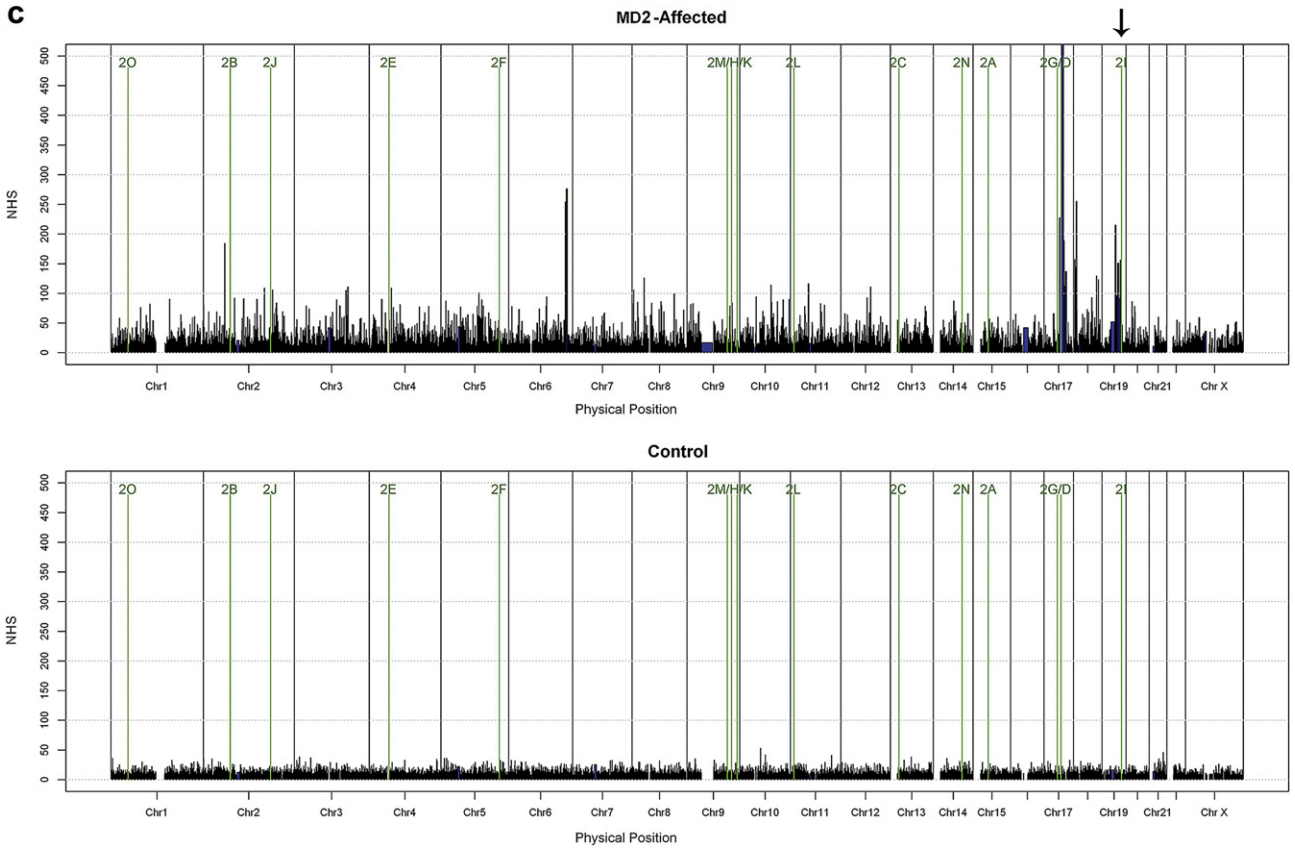

Fig. 1. (*continued*).

unaffected sibs using our self developed tool to detect the homozygosity profiles of each individual. As can be seen in Fig. 1a, there is only one peak present in the affected sibs which overlaps with one of the known LGMD2 loci. This peak is located on chromosome 15 (37607895–62926989 bp) and contains the *CAPN3* gene. *CAPN3* sequencing identified the known homozygous c.483delG (p.Ile162SerfsX17) mutation in exon 3 [8] in the two affected children, for which the parents were heterozygous (Fig. 2a). The healthy sibs were not homozygous for this mutation.

3.2. Family MD2

At 17 years this 26 year old female first noticed problems in climbing stairs and weakness in the proximal upper limbs muscles and mild to moderate cardiomyopathy appeared subsequently. There was no family history regarding any neuromuscular diseases. On examination calf hypertrophy was present. Muscle weakness and wasting were restricted to the proximal limb musculature and predominated in the lower limbs. She walked with a waddling gait and had mild scapula winging. Rippling, mounding and percussion induced rapid muscle contractions were not present. CK levels were elevated up to 2000 U/l and EMG confirmed a chronic myopathy. Muscle biopsy at age 23 showed severe myopathic changes (Fig. 3aA). Caveolin-3 immunostaining and western blotting indicated a complete loss of the caveolin-3 protein expression, whereas other muscle proteins were normal (Fig. 3b). However, sequencing of *CAV3* and *PTRF*, which had been reported to be associated with secondary caveolin-3 deficiency [6] failed to detect a pathogenic mutation.

Subsequently, a more detailed family history revealed that the parents of the patient were second degree cousins. Analysis of the 10 K SNP array genotypes of the patient and her healthy sib identified two large homozygous regions at chromosomes 17 (36518826–61670208 bp) and 19 (34206067–54914726 bp) corresponding to the LGMD2D [OMIM 608099] and LGMD2I [OMIM 607155] loci (Fig. 1b). Additional analysis of the denser 250 K SNP array did not exclude any of these loci and did not detect further homozygous regions corresponding to known LGMD2 loci (Fig. 1c). Re-examination of the patient's muscle biopsy revealed pathologically aberrant glycosylation of α-dystroglycan on the sarcolemma compared to a control muscle by immunoblotting (Fig. 3b) and immunohistochemistry (Fig. 3aB, aC). Finally, sequencing of the fukutin related protein gene (*FKRP)* identified the common c.826 C > A; (p.Leu276Ile) mutation (Fig. 2b) thus establishing the diagnosis of LGMD2I [17]. MRI studies of the proximal muscles of the upper and lower limbs were consistent with previous findings in LGMD2I [3].

4. Discussion

Individual diagnosis and classification of LGMD2 patients is challenging due to considerable intra- and inter-familiar clinical variability and genetic allelic and non-allelic heterogeneity with 15 disease genes known so far. In addition, an extensive diagnostic work-up including invasive muscle biopsy is usually required [1,5]. In this study we present the successful application of SNP-array based whole genome homozygosity mapping in the molecular genetic diagnosis of LGMD2. We emphasize this form of indirect DNA analysis as the first step in the approach to diagnose patients from families with known or suspected parental consanguinity, because it is fast, inexpensive, and amenable to high-throughput setting. In principle, the causality of several known LGMD2 genes

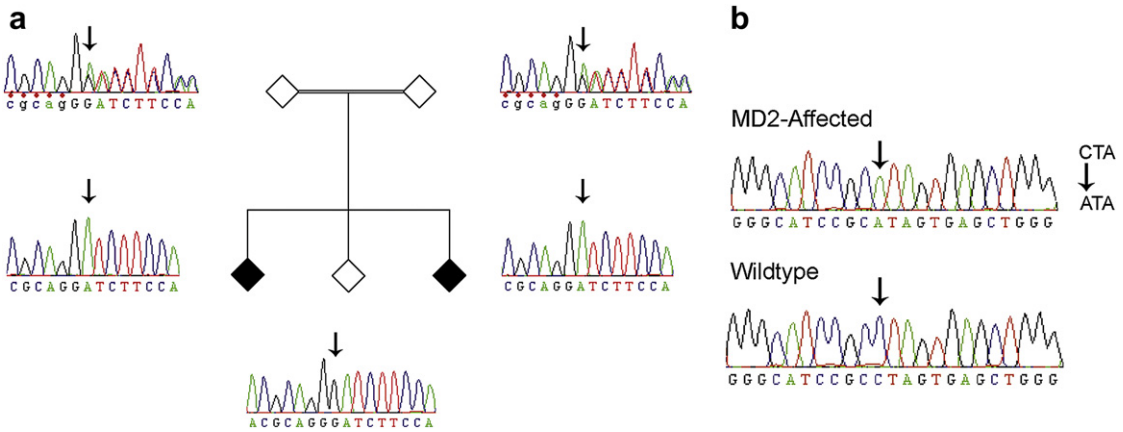

Fig. 2. Sequences of the *CAPN3* (exon 3) and the *FKRP* (exon 4) gene. a. Part of the pedigree of family MD1, showing the parents (first cousins) carrying the heterozygous c.483delG mutation (p.Ile162SerfsX17) and the two affected children with the homozygous mutation, as well as one child without a sequence change at this position (see arrows). b. Part of the sequence of patient MD2 carrying the homozygous c.826 C > A mutation; (p.Leu276Ile, rs28937900) (see arrow).

can be excluded with high probability in patients that do not show extended homozygosity at these loci.

Because the patients included in this study originated from inbred populations LGMD2 caused by a homozygous mutation in one of the known LGMD2 genes was the most likely underlying genetic event. Whole genome homozygosity mapping using the 10 K SNP array was straightforward in the three patients examined here. In both families statistical and visual analysis revealed several homozygous intervals. A single large homozygous region, at the LGMD2A [OMIM 253600] locus, was seen in both patients from family MD1, without genetic linkage and haplotype analyses, enabling a fast, non-invasive diagnosis following the sequence analysis of *CAPN3*.

The more distant parental relationship reduced both the number and the size of homozygous regions in patient MD2 compared to patients from MD1. However, two homozygous regions overlapping with LGMD2 loci, were considered identical by descendent from a common ancestor because of their genomic size and extent in the number of homozygous markers (Fig. 1). Identification of a common, homozygous *FKRP* [17] mutation established a diagnosis of LGMD2I, which was confirmed by aberrant muscle α-dystroglycan staining (Figs. 2b and 3aB, b).

Notably, the correct diagnosis in patient MD2 was delayed due to the absent caveolin-3 protein expression leading to the initial suspicion of LGMD1C [OMIM 607801]. Although secondary protein deficiency documented by immunohistochemistry in muscles of LGMD patients is not unusual and may be misleading in the further diagnostic process [12], the finding of caveolin-3 deficiency is surprising, as has been demonstrated by a study suggesting that caveolin-3 protein deficiency is a highly sensitive and specific marker of primary caveolinopathy [4]. However, secondary caveolin-3 deficiency has recently been reported in patients with lipodystrophy and muscular atrophy carrying mutations in *PTRF* [6]. The underlying mechanism of the secondary caveolin-3 deficiency in our *FKRP* patient remains elusive, but may be due to the altered α-dystroglycan glycosylation, which might interfere with the correct localization of caveolin-3 at the sarcolemma. Therefore we suggest that LGMD2I should be considered in patients with absent caveolin-3 expression in skeletal muscle and normal results on *CAV3* sequencing.

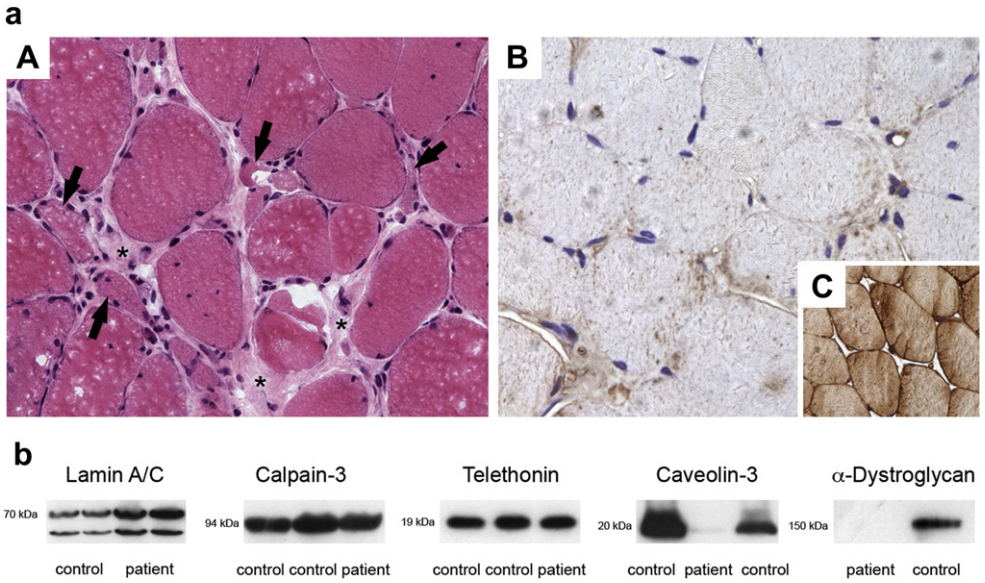

Fig. 3. a. Muscle biopsy of patient MD2 shows severe myopathic changes with variation in fibre size (arrows), necrosis, regenerating fibres, and an increase in endomysial connective tissue (asterisks) (A, H&E). Immunohistochemistry reveals a severe reduction in labelling of the glycosylated epitope of α-dystroglycan (B, α-DG) compared to healthy control (C, α-DG). Magnification: (A) ×200; (B, C) ×400. b. Immunoblotting for α-DG could not detect the glycosylated protein with molecular mass of 150 kDa (D, α-DG, VIA4) and confirmed the absence of caveolin 3, whereas calpain 3, lamin A/C, and telethonin were normal.

A recent study has demonstrated that high-density SNP homozygosity mapping can also successfully be applied to non-consanguineous single individuals with rare autosomal recessive diseases, such as LGMD2, considering the hypothesis that the disease is caused by a homozygous mutation located within a homozygous haplotype, being identical by descent from an unknown common ancestor [7]. Homozygous disease-causing mutations could be detected in single cases of outbred populations within homozygous areas often larger than 2 Mb in size [7]. On the other hand, homozygous genomic segments measuring up to 4 Mb were not uncommon in individuals from outbred populations [10]. Although application of the 10 K SNP array was sufficient to detect the disease-related homozygous regions in the patients examined here, only higher density SNP arrays might allow the detection of the disease-related homozygous segments in cases of more distant or suspected parental relationship.

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